The validity of the observation that dronedarone reduces cardiovascular hospitalization would have been strengthened if the trial had documented systematically the underlying reasons for hospitalizations (typically hemodynamic instability, exacerbation of heart failure, anticoagulation, or cardioversion) and the expected attendant improvement in symptom status and quality of life. Coupled with the lack of external adjudication (that minimizes the vulnerability to cardiovascular versus noncardiovascular misclassification errors, particularly in trials that span geographic regions and clinical practice settings) (3,4) and the exploratory nature of the analysis (given the pre-specified hierarchical sequential plan), these limitations serve not only to undermine the clinical relevance of this finding, but also to raise questions about the overall quality of the data, and ultimately the reliability of the findings.

The original report mentions 1 amendment dated March 8, 2006, to alter the enrollment criterion to include older subjects (2). No further protocol changes are mentioned, including the amendment dated August 25, 2006, to increase the sample size from 3,700 to 4,300, nor is any reason given for the extension of the sample size from 4,300 to 4,628. We do not doubt these protocol changes were done blindly, without knowledge of any emerging treatment effects. However, we are intrigued that investigators stopped at 255 deaths, 5 short of achieving the protocol-specified goal of 260 deaths. Nonetheless, these protocol changes should have been reported in a transparent manner and appropriate caution should have been urged in interpreting cardiovascular death results as being exploratory, given the rules of engagement of a hierarchical sequential analysis plan. Instead, the published conclusion that the drug reduced cardiovascular deaths is highly misleading, when in reality that benefit was not significant under the original plan (1). Although no malfeasance is implied, we nonetheless feel strongly that changing rules in the middle of the trial is antithetical to the principles of good clinical trial practice. Moreover, the mechanisms that underlie dronedarone's reduction of cardiovascular death remain unclear. Death resulting from stroke, ventricular arrhythmia, or heart failure was not impacted favorably by dronedarone (2). Did the associated reductions in acute coronary syndromes—a post-hoc observation—account for this finding, or was this merely the play of chance? In the end, the ATHENA trial was not designed to answer these questions, and the observed reduction in cardiovascular death is at best exploratory and hypothesis generating, requiring confirmation in subsequent studies.

The authors have raised issues with our meta-analysis. The objective was not solely to estimate an overall measure of effect (a synthesis-centric goal), where it is appropriate to question whether certain studies should be combined, but rather to explore the reasons for differences between the studies (an analysis-centric goal) to place the evidence in its proper context. The results are insightful because they provide reassurance about dronedarone's safety in the target population (1). The weighting is described in the figure legend (1), and adjusting for patient-years of exposure did not materially change the summary relative risk estimate. Finally, we acknowledge the typographical error regarding the mean follow-up in the ANDROMEDA (ANti-arrhythmic trial with DROnedarone in Moderate to severe congestive heart failure Evaluating morbidity DecreAse) trial, which had no impact on our analysis.

Rather than missing the forest for the trees, we present the evidence in an objective and unembellished manner. Although the truth can be determined by each reader, the plain fact, in our opinion, is that dronedarone has very modest efficacy as an antiarrhythmic agent, and based on the current evidence, its use for the treatment of nonpermanent atrial fibrillation or atrial flutter can be supported only as a second- or third-line agent in individuals who are not able to tolerate amiodarone or other first-line agents recommended by the guidelines.

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REFERENCES

1. Singh D, Cingolani E, Diamond GA, Kaul S. Dronedarone for atrial fibrillation have we expanded the antiarrhythmic armamentarium? J Am Coll Cardiol 2010;55:1569–76.
2. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668–78.
3. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction—results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992;327:669–77.
4. Mahaffey KW, Harrington RA, Akkerhuis M, et al., for the PURSUIT Investigators. Disagreements between central clinical events committee and site investigator assessments of myocardial infarction endpoints in an international clinical trial: review of the PURSUIT study. Curr Control Trials Cardiovasc Med 2001;2:187–94.

The Concept of the Metabolic Syndrome

Is It Dead Yet?

The main finding of the case-control study by Mente et al. (1) is that the risk of myocardial infarction associated with the diagnosis of metabolic syndrome (MS) is no greater than that of the sum of its individual components. However, this interpretation is solely based on a finding of similar effect sizes (odds ratio) associated with MS and previously diagnosed (and/or treated) diabetes mellitus or hypertension. The authors note that, in this study (as in many other studies), both hypertension and diabetes frequently coexisted. Moreover, they suggest that the patients with hypertension or diabetes were more likely to have at least 1 additional component of MS present (most commonly, central obesity: 71%). Therefore, it is not surprising that the odds ratio associated with each of them in separate regression models was found to be similar to that obtained by the use of MS, as patients with both diabetes and hypertension also had clustering of other individual components. We believe it would be more informative to describe the effect sizes associated with those with only diabetes or only hypertension, when comparing them with those associated with the presence of MS. However, to assess whether the sum of the risk associated with individual components is greater than that associated with the presence of MS, it may be better to estimate the risk of myocardial infarction associated with MS, after adjusting for all its individual components (when used as continuous variables) in a regression model.

Furthermore, a review of current literature suggests that the approach of using only effect sizes when comparing the utility of risk factors may be obsolete—particularly in light of more efficient statistical approaches such as net reclassification index and incremental discrimination index (2,3)—the techniques that enable comparisons based on number of subjects correctly allocated with the enhanced risk or not.

However, we agree that despite these further analyses, the eventual interpretation may remain unchanged, as evidenced by findings of a recent study (4) among >19,000 hypertensive patients, where there was an absence of any synergy among the individual components of MS on the risk of coronary outcomes associated with MS. However, in that study, the risk of stroke and all-cause mortality associated with MS, independent of its components, was found to be significant. We believe these apparent contradictions in the current literature are likely to be minimized by interrogating prospective data, to evaluate whether the risk of myocardial infarction (both in terms of magnitude and the number of patients correctly identified) is more closely associated with MS or with the presence of each of the individual risk factors, separately and in combination.

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REFERENCES

1. Mente A, Yusuf S, Islam S, et al. Metabolic syndrome and risk of acute myocardial infarction: a case-control study of 26,903 subjects from 52 countries. J Am Coll Cardiol 2010;55:2390–8.
2. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. J Am Coll Cardiol 2009;54:1209–27.
3. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72, discussion 207–12.
4. Gupta AK, Dahlof B, Sever PS, Poulter NR. The metabolic syndrome, independent of its components, is a risk factor for stroke and death, but not for coronary heart disease among hypertensive patients in the ASCOT-BPLA. Diabetes Care 2010;33:1647–51.

Reply

Drs. Gupta and Poulter raise an interesting point about our study (1) and about estimating the risk of myocardial infarction (MI) associated with metabolic syndrome (MS), after adjusting for all its individual components (as continuous variables). The idea of controlling for all components and MS simultaneously to assess each of the effects comparatively seems intuitive. However, there are statistical assumptions in constructing such a model. Controlling for component factors that were used to define MS would likely substantially alter the association between MS and MI risk. Indeed, when adjusting for all of the individual MS components, the odds of MS on MI risk is <1 (odds ratio: 0.79; 95% confidence interval: 0.68 to 0.91); however, the effects of diabetes mellitus (odds ratio: 2.52; 95% confidence interval: 2.24 to 2.83) and hypertension (odds ratio: 2.22; 95% confidence interval: 2.05 to 2.39) remain robust after simultaneous adjustment. Prior investigations have used a similar approach to that of our study in assessing the effects of MS and component factors (2,3).

We agree that alternative analytical approaches may be used to determine the agreement between MS and component factors classification versus MI (e.g., net reclassification). However, this approach is usually applied to prospective cohort data, and not to retrospective case-control data. Nonetheless, as the investigators recognize, the general pattern of results and eventual interpretation is unlikely to change. Moreover, an important advantage of estimating the effect size is that it may be used to estimate population attributable risk (PAR), an approach used previously in the first INTERHEART study (a global case-control study of risk factors for acute myocardial infarction) paper, which showed that 90% of risk of MI is explained by 9 modifiable risk factors (4). An assessment of the PAR of MS on MI is particularly important in the current study, since the use of a dichotomous definition of MS based on ≥3 risk factors leads to a substantially lower prevalence of MS than its component factors (e.g., 10% for MS compared with 19.6% for diabetes and 23.4% for hypertension). This finding partly explains our observation that the PAR of MS is substantially lower than the PAR of several component factors considered separately, including diabetes and hypertension, and indicates that MS accounts for a smaller number of MI cases in a population compared with several of its constituent components. Thus, our findings highlight an important limitation of MS diagnosis.

We also agree that a cohort study might provide more rigorous data. However, an important strength of the INTERHEART study is that it is a large international study of 52 countries using a standardized protocol, and it is the first large study to show that the risk of MI associated with MS is qualitatively similar across sex, global regions, and ethnic groups. A cohort study with similar objectives would require an enormous sample size and 2 decades of follow-up. Although not impossible, such a study would be extremely costly to conduct.

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REFERENCES

1. Mente A, Yusuf S, Islam S, et al. Metabolic syndrome and risk of acute myocardial infarction: a case-control study of 26,903 subjects from 52 countries. J Am Coll Cardiol 2010;55:2390–8.
2. Iribarren C, Go AS, Husson G, et al. Metabolic syndrome and early-onset coronary artery disease: is the whole greater than its parts? J Am Coll Cardiol 2006;48:1800–7.
3. Nabipour I, Amiri M, Imami SR, et al. The metabolic syndrome and nonfatal ischemic heart disease: a population-based study. Int J Cardiol 2007;118:48–53.
4. Yusuf S, Hawken S, Ounpuu S, et al., for the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.